

## Lysosome homeostatic recovery induced by glutamine

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Summer 2018

Lysosomes are the organelle responsible for degrading and recycling macromolecules within the cell. During nutrient deprivation, cells activate the autophagy pathway to perform this degradation and recycling using acid hydrolases. Upon starvation and blocking lysosomal activity using chloroquine to deactivate the acid hydrolases, enlarged, swollen lysosomes accumulated in the cell. Surprisingly, the addition of the amino acid glutamine dissipated these enlarged lysosomes. We investigated this phenomenon through manipulation of the mechanistic target of rapamycin (mTOR), specific autophagy genes ATG5 and ATG7, and the transcription factor EB (TFEB) responsible for lysosome biogenesis. It was discerned the movement of TFEB between the nucleus and cytoplasm correlated with the presence of enlarged lysosomes and glutamine-dissipated lysosomes, respectively. However, when performing a knockdown of TFEB to reduce its presence in the cell, enlarged lysosomes were still able to form without TFEB involvement. This suggests a unique mechanism by which lysosome homeostasis is regulated and recovered under certain conditions with the assistance of glutamine. Recently, we investigated a possible mechanism of enlarged lysosome dissipation. Specifically, we looked at SNAT7 and SNAT9 genes. These genes encode for sodium channels that also transport the amino acid glutamine. We performed a knockdown of the genes to see if enlarged lysosome dissipation occurred through this mechanism. Our results showed the removal of these channels did not inhibit enlarged lysosome formation or recovery upon the addition of glutamine. Following work will look at calcium channels on the lysosome and endoplasmic reticulum (ER) to see if these, as opposed to the sodium channels, are involved in this novel mechanism.

The investigation of the mechanism behind these enlarged lysosomes will help elucidate facts in the study of CLN5 disease, a subtype of neuronal ceroid lipofuscinosis (NCLs), a neurodegenerative disorder that mainly affects children. The gene product, CLN5 protein, resides in the lumen of the lysosome. While the function of CLN5 protein is unknown, our data indicate the CLN5 protein could be involved in this enlarged lysosome phenomenon, as CLN5-deficient cells cannot form these enlarged lysosomes under the same starvation conditions. With more investigation, we hope to discover this connection between enlarged lysosomes and CLN5 disease.